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# Vitamin A Supplementary Effect on Immunologic Profiles in Tuberculosis Patients

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ABSTRACT

***Background:*** *The effects of vitamins on human immune system have been well studied. Vitamin A deficiency and its effects on immune system in pulmonary tuberculosis (TB) patients have been established. This study was carried out to evaluate vitamin A supplementary effect on immunologic profile of tuberculosis patients.*

***Materials and Methods:*** *In a double-blind clinical trial, thirty-five patients with confirmed pulmonary tuberculosis were included. The case group received vitamin A injection, 50000 IU, every 10 days for two months along with standard treatment of TB; the control group received only anti-TB drugs. Immunologic profiles including CD3+, CD4+, CD8+, CD4+/CD8+, CD19+, HLA-DR, CD16+56+, and plasma vitamin A as well as nutritional status were assessed in both groups primarily and two months after above-mentioned treatments. Data were analysed using SPSS software version 10.*

***Results:*** *The study showed that there were not significant differences in mean(± SD) of age, body weight, height, body mass index (BMI), fat thickness and vitamin A plasma level between the vit A-receiving and control groups.*

*The mean of peripheral blood CD3+ showed significant increase in patient-control group [71.8 ±7.9 % lymphocytes (after supplementation) compared with 68.3 ±10.7% (before supplementation); p= 0.014.]. This was also true about CD4+ (p= 0.001). CD4+ to CD8+ ratio and the mean of CD19+ showed significant decrease in the patient control group and the vit A-receiving group, respectively (p= 0.002 and p= 0.04, respectively).*

*In contrast, there was an increased significant difference for CD+16+56$^{+}$ mean in the above-mentioned groups which was more prominent in the vit A- receiving group (p=0.038). The means of HLA-DR and CD8$^{+}$ did not show significant differences in both groups before and after supplementation.*

***Conclusion:*** *It seems that vitamin A supplementary effects on the quality of lymphocytic markers are remarkable. However, further studies should be performed regarding immunologic response quality.* ***(Tanaffos 2005; 4(14):53-60)***

***Key words:*** *Tuberculosis, Vit A supplementation, Immunologic profile*

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## INTRODUCTION

Tuberculosis (TB) is an established well- known disease (1). Numerous studies have shown not only a synergic relationship between malnutrition and TB but also the role of malnutrition in suppressing immune system and disease severity.

Usually, severe malnutrition is accompanied with infection (2). Several elements including vitamins A, C, D, E, $B_{12}$, riboflavin, iron, zinc, and selenium interfere with the immune system; therefore, they affect host susceptibility to infection. Recently, it has been shown that individuals with inappropriate dietary intake have impaired immune responses, and the majority of abnormalities are detected in complement system, phagocytes and secretory mucus responsible for secretion and absorption of antibodies.

Furthermore, the lack of each nutrient can impair immune responses alone and relapse may occur during this process (3). Investigations show that vitamin supplementation can improve cell-mediated immunity efficacy which is presented by T cell and lymphocyte proliferations (4). Vitamin A deficiency in TB adult patients has been detected (5).

Vit A Insufficiency increases bacterial penetration into respiratory epithelial cells (6). In addition, the need for vit A is increased during infection due to increased metabolism (7). Also, vit A and zinc supplementations improve nutritional state and therapeutic effects of anti-TB drugs. It has been recently known that retinoic acid can prevent mycobacterial proliferation in macrophages (8).

Some vitamins have an important role in protecting immune system, even their marginal lack may impair immune response. On the other hand, their supplementations with higher amounts of daily recommended doses increase humoral and cell-mediated immunities (9).

In most diseases including cardiovascular disease, cancer, inflammatory and infectious diseases, free radicals are released having a destructive role within the body. They can be also produced by immune cells. The aim of immune system in this manner is impairing the action of invasive organisms, although these potent oxidants like free oxygen radicals can impose additional stress on the immune system resulting in reduction of reaction against the organism. As a whole, the body has a complex defence system including vitamins and enzymes which have protective effects on free radicals directly or indirectly (10).

Regarding the therapeutic advantages of vit A in the improvement of TB patients and finding out appropriate procedures to control and improve the disease, we decided to evaluate vit A supplementary effect on immunologic profile of TB patients.

## MATERIALS AND METHODS

This study was divided into two phases: the first was performed as a cross-sectional study on fifty TB patients (patients group) and fifty healthy individuals (control group). The second, it was carried out as a double-blind randomized clinical trial on TB patients alone.

Initially, pulmonary TB patients hospitalized in this center (Masih Daneshvari Hospital) between September 2003 and February 2004 were selected as the case group whose diagnoses based on World Health Organization (WHO) recommendations, clinical, radiologic and bacteriologic criteria. Inclusion criteria were hospitalized patients older than 14 years old with recent diagnosis of pulmonary TB, and exclusion criteria were pulmonary TB patients with negative smear and culture and those

with extra- pulmonary TB and also Afghans. For each case, a questionnaire of 24-hour nutritional diet was filled out and the amount of food used by each person was changed to gram by using alteration indices and household scales (11). Then it was calculated by food processor II software.

Body weight and height were measured and body mass index (BMI) was calculated in $kg/m^2$. Patients with BMI<18.5, 18.5-24.9, 25-29.9 and ≥ 30 were considered as low weight, normal, over weight and obese, respectively (12). After obtaining an informed consent form each patient, a blood sample was taken for measuring serum vitamin A level and immunologic assay. Standard blood flow-cytometry was performed to measure cell components such as CD3+, CD4+, CD8+, CD4+/CD8+, $CD16+56^+$, CD 19+ and HLA-DR. After that, 50 age and sex-matched first degree relatives without TB were selected as healthy control group. Nutritional status and vit A plasma level were assessed for them, as well. At second phase, 15 patients were randomly selected among the case group to receive vitamin A (vit A-receiving group), administrating by the injection of 50000 IU doses each 10 days for two months along with standard TB treatment. Twenty TB patients matched in age, sex and type of the disease, were selected as patient- control group and only received anti-TB drugs. After 8 weeks, blood samples were taken from the vitamin A receiving group and patient control group. Additionally, vitamin A plasma level, immunologic profiles, 24-hour recall and BMI were evaluated and sputum smear was performed for BK using Ziehl-Neelsen staining in a reference laboratory (which is located in our center). In addition, sputum culture in Lowenstein Jensen medium and sensitivity test were also carried out using proportion method. Flow-cytometry was performed by obtaining 2cc of blood from peripheral vessels by dual colour panel conjugated antibody using fluorescein isothiocyanate (FITS) and phycoerythrin (PE) staining (made by Becton Dickinson company). The used antibodies included CD3+/CD4+, CD3+/CD19+, and $CD3+/CD16+56^+$. Cell count analysis was performed by flow-cytometry technique using SimulSET software and FACS caliber.

Vitamin A was measured using a method described by Biri et al. A high performance liquid chromatography (HPLC) system (Model: 1110 Cecil); was utilized using Cecil (data control) software. The column used in this system was Spheriosorb 5(2), 250×4.60 mm. Serum vitamin A levels lower than 30 μg/dl, 30-80 μg/dl and higher than 80 μg/dl were considered as low, normal and high, respectively (13).

This project was approved by the ethic committee of Shaheed Beheshti University of Medical Sciences and the written consent was obtained from all understudy patients.

Data were analysed using SPSS software ver.10. Quantitative variables were analysed by chi-square test (and Fisher's exact test, if necessary). T- student test (for data with normal distribution) and Mann-Whitney U test (for those without normal distribution) were used for continuous variables. P-value less than 0.05 was considered as significant.

## RESULTS

In this study one hundred individuals were included in whom 50 (60% men, 40% women) were considered as case (patient) group and 50 (48% men, 52% women), were considered as control group. There was no significant difference between the two groups in this issue (p>0.05). Table 1 shows mean of

age, weight and height, BMI, and triceps subcutaneous fat pad diameter (TSF) in the two groups. Regarding these results, 36%, 50% and 14% of cases in the patient (case) group had BMI<18.5 kg/m$^2$ (low weight), 18.5-24.9 kg/m$^2$ (normal) and 25-29.9 kg/m$^2$ (overweight), respectively, whereas in the control group, 12%, 58%, 22% and 8% of cases had BMI<18.5, 18.5-24.9, 25-29.9 and ≥30 (obese), respectively. There was a statistically significant relationship between BMI and TB involvement (K2 test; p= 0.011).

Table 1. Mean (±SD) of age, weight, height, BMI and triceps subcutaneous fat thickness in case and control groups.

| Group | Case | Control | P-value |
|---|---|---|---|
| Statistical index variable | X±SD | X±SD | |
| Age (y) | 51.4±18.5 | 45.5±14.4 | 0.07 |
| Weight (kg) | 53.5±10 | 68.1±11.8 | 0.000 |
| Height (cm) | 161.2±10 | 163.3±9.2 | 0.3 |
| BMI•(Kg/ m2) | 20.7±3.6 | 23.7±1.4 | 0.000 |
| TSF *( cm) | 12.1±2.8 | 14.1±4.6 | 0.011 |

•BMI: Body Mass Index

*TSF: Triceps Subcutaneous fat thickness

As shown in table 2, there were significant differences in mean (±SD) of calorie, carbohydrate, fiber, protein, fat, vitamin E, vitamin A, thiamine, riboflavin, niacin, pantothenic acid, pyridoxine, folic acid, iron, calcium, sodium, potassium, phosphorus, copper, zinc and selenium intakes between the case and control groups. Conversely, vitamin C and cobalamin intakes did not show significant differences between the two groups. Vitamin A plasma level was 30.2±9.5 μg/dl and 41.1±10.9 μg/dl in the case and control group, respectively, which was significant (p=0.000). Results showed that 54% and 46% of cases in the case group had plasma levels of vit A <30 μg/dl (low) and 30-80 μg/dl (normal), respectively. On the other hand, 16% and 84% of cases in the control group had low and normal plasma levels of vitamin A, respectively. There was a statistical significant relationship between different levels of vitamin A and TB involvement (K2 test; p= 0.000). In the second phase, there were not significant differences in mean (±SD) of age, weight, height, BMI and TSF between the vit A- receiving and patient-control groups (table 3).

Table 2. Mean (±SD) of calorie and daily nutritional element in the case and control groups.

| Group | Case | Control | P-value |
|---|---|---|---|
| Statistical index variable | X±SD | X±SD | |
| Calorie | 1272.7±332.1 | 1767.7±436.8 | 0.000 |
| Carbohydrate | 181.5±54 | 252.6±68.8 | 0.000 |
| Fiber | 6.7±3 | 11.1±7.7 | 0.000 |
| Protein | 39.8±10.3 | 56.3±21.7 | 0.000 |
| Total fat | 44.6±16.2 | 60.7±20.6 | 0.000 |
| Vit A, carotene | 598.5±145 | 973.2±215.5 | 0.000 |
| Vit A | 312.6±252.5 | 609.1±349.5 | 0.021 |
| Vit E | 1.9±0.9 | 2.3±0.8 | 0.013 |
| Vit C | 43.1±50.6 | 45.7±28.3 | 0.054 |
| Thiamine | 0.9±0.3 | 1.2±0.4 | 0.000 |
| Riboflavin | 0.7±0.2 | 1±0.7 | 0.030 |
| Niacin | 10.8±3.1 | 14.5±5.3 | 0.000 |
| Pantothenic acid | 1.4±0.6 | 2.2±0.9 | 0.000 |
| Pyridoxine | 0.9±0.5 | 1±0.4 | 0.000 |
| Cobalamin | 1.2±0.7 | 6.6±2.1 | 0.109 |
| Folic acid | 53.1±45.1 | 84.9±58.1 | 0.003 |
| Iron | 13±4 | 20.1±7.2 | 0.000 |
| Calcium | 549.2±287.7 | 740.6±395 | 0.021 |
| Sodium | 410.5±267 | 712.5±338 | 0.044 |
| Potassium | 1572.8±672.6 | 1920.4±735.4 | 0.000 |
| Phosphorus | 433.5±132.9 | 552.7±163.5 | 0.000 |
| Copper | 0.5±0.2 | 0.7±0.4 | 0.000 |
| Zinc | 2.6±1.3 | 3.5±1.3 | 0.001 |
| Selenium | 36.9±16.5 | 56.6±25.9 | 0.000 |

Table 3. Mean (±SD) of age, weight, height, BMI and TSF in vit A- receiving and patient-control groups.

| Group | Vit A- receiving (n=13) | Patients control (n=16) | P |
|---|---|---|---|
| Statistical index variable | X±SD | X±SD | |
| Age (y) | 50.7±20.4 | 52.0±18 | 0.977 |
| Weight (kg) | 50.3±8.7 | 55.7±9.8 | 0.284 |
| Height (cm) | 160.4±10.6 | 161.4±10.5 | 0.944 |
| BMI• (Kg/ m2) | 19.7±3.9 | 21.4±3 | 0.344 |
| TSF* ( cm) | 12.7±3.7 | 12.5±1.9 | 0.210 |
| Plasma level of Vit A | 30.5±8.57 | 28.8±7.8 | 0.334 |

•BMI:Body Mass Index,*TSF:Triceps Subcutaneous fat thickness

As shown in table 4, there was not any significant difference in the mean of daily calorie intake of patient-control group before and after supplementation. The opposite was true for vit A-receiving group. In addition, the mean of daily calorie intake, dietary protein and vit A did not show significant differences between the two-patient groups pre and post- interventionally.

Table 4. Mean (±SD) of dietary calorie, protein and Vit A in the patient-control and vit A receiving groups (pre and post intervention)

| Group Dietary elements/ nutrients | Vit A- Receiving (pre intervention) | Vit A- Receiving (post- intervention) | P | Patient- control (pre intervention) | Patient- control (post- intervention) | P |
|---|---|---|---|---|---|---|
| | X±SD | X±SD | | X±SD | X±SD | |
| Calorie | 1383.6 ±318.7 | 1578.6± 435 | 0.012 | 1265.2± 392.5 | 1341.3± 362.2 | 0.107 |
| Protein | 39.7± 6.2 | 53.6± 19.3 | 0.161 | 38.6± 9.9 | 43.6± 15.8 | 0.098 |
| Vit A | 351.1± 335 | 254.9± 138.6 | 0.753 | 293.6± 238.7 | 324.7± 165.2 | 0.519 |

The mean of vitamin A plasma level were 38.6±10.06 μg/dl and 30.4±7 μg/dl after supplementation and 30.5±8.57 μg/dl and 28.8±7.8 μg/dl before supplementation in vitamin A receiving group and patients control group, respectively which showed statically significant increase only in the first group (p=0.003).

The means of peripheral blood CD3+ and CD4+ showed significant increases in the patient-control group (p=0.014 and p=0.001, respectively) but it was true about CD4+ mean in vit A- receiving group (p=0.222, table 5).

Table 5. Mean (±SD) of immunology profiles in vit A-receiving group and patient control group (pre and post intervention).

| Group Immunologic profile | Vit A- Receiving (pre intervention) | Vit A- Receiving (post- intervention) | P | Patient- control (pre intervention) | Patient-control (post- intervention) | P |
|---|---|---|---|---|---|---|
| | X±SD | X±SD | | X±SD | X±SD | |
| CD $_{3}^{+}$ | 71.1± 9.1 | 76.5± 7.7 | 0.053 | 68.3± 10.7 | 71.8± 7.9 | 0.014 |
| CD $_{4}^{+}$ | 44.9± 9.6 | 40.7± 7.7 | 0.202 | 42.6± 6.6 | 46.1± 5.2 | 0.001 |
| CD $_{8}^{+}$ | 39.1± 9 | 36.3± 11.9 | 0.241 | 33.6± 7.9 | 33.5± 8.1 | 0.576 |
| CD $_{4}^{+}$/ CD $_{8}^{+}$ | 1.3± 0.6 | 1.2± 0.5 | 1.000 | 1.5± 0.5 | 1.4± 0.5 | 0.002 |
| CD $_{19}^{+}$ | 16.1± 5.6 | 12± 4.4 | 0.040 | 14.1± 7.4 | 13.4± 5.1 | 0.804 |
| CD $_{16+56}^{+}$ | 16.7± 10.8 | 20.6± 12 | 0.028 | 15.5± 5.7 | 17.9± 5.7 | 0.013 |
| HLA-DR | 11.5± 4.2 | 12.9± 10.3 | 0.858 | 11.3± 6.1 | 13.5± 5.9 | 0.058 |

As shown in table 5, there were decreases in CD4+/ CD8+ and CD19+ means in the two patient groups as they were statistically significant in patient control group and vit A-receiving group, respectively. (p=0.002 and p=0.04, respectively). In contrast, the means of CD16+56$^{+}$ were 20.6±12 and 17.9±5.7, post-interventionally and 16.7±10.8 and

15.5±5.7, pre-interventionally, in vit A-receiving group and patient-control group, respectively, which showed statistically significant increases especially in the first group (p=0.013 and p=0.028, respectively). HLA-DR and CD8+ means did not show significant differences between the two patient groups.

## DISCUSSION

The present study showed that vit A plasma level in TB patients was significantly decreased in comparison with healthy control group (p=0.000) which confirmed Madebo et al's study in 2003. They demonstrated that the plasma level of vitamin A in 25 Ethiopian TB patients was significantly decreased comparing to control group (14).

A study conducted by Plit et al. in 1998 on 41 patients with pulmonary TB, showed that plasma level of beta carotene was low in them, although administration of anti-TB drugs up to 6 months returned its level to normal (15). Mugusi et al. (16) described a low vit A plasma level in TB patients involved with human immunodeficiency virus (HIV). A study conducted by Rwangabwoba et al. (17) confirmed this result, as well (p<0.07).

The second phase of the present study showed that vit A supplementation could increase its plasma level significantly (p=0.003) but treatment with anti-TB drugs did not have such effect on the patient control group. This was in accord with other studies too (14). However, this increase was expected in vitamin A-receiving group because vitamin A is a fat-soluble agent and accumulates in the body (12).

Fortes et al. (18) showed that vit A supplementation of 800 μg/dl can cause significant increase in the number of CD4+ T cells (p=0.012). In addition, Ertesvag et al. (19) demonstrated that retinoic acid can stimulate CD4+ T cells and induce T cell proliferation, depending on timely addition of this agent. In other words, increasing period of vit A administration may cause definitive changes in CD4+ T cells. Thus, we suggest that the period of therapy with vit A must be increased to more than 2 months.

Fortes et al. showed that vitamin A supplementation (800 μg retinol palmitate) did not induce a significant alteration in cytotoxic T lymphocyte (CD8+) which confirmed our results (20).

In 1999, Dawson et al. (21) demonstrated that CD4+/CD8+ ratio is significantly higher in the mice treated with vitamin A supplementation rather than those with vitamin A deficiency (p<0.005).

In animal studies, vitamin A deficiency induces a shift from type 2 (humoral) cytokine to type 1 (cellular) cytokine; although, there are no similar data for humans. Retinoic acid can cause down-regulation of interferon- gamma (IFN-γ) and type 1 cytokine genes expressions. Lack of this material induces overproduction of IFN-γ, and subsequent reduction of interleukin-5 (IL5),(which is a type 2 cytokine that stimulates eosinophils and makes a relationship between T cell activation and eosinophilic infiltration); and IL-10, (which is also a type 2 cytokine that shifts immunologic profile to type 2 profile) (22, 23).

In a study conducted by Jason and coworkers in Malawi, Africa on 149 children over than 13 years of age (where Mycobacterial infections and malaria are endemic), a correlation was found between vit A plasma levels and type 2 cytokines in children with vit A deficiency who had lower production of IL-10 (but higher TNF-α production) by monocytes and increased number of CD3+ cells in comparison with those without this deficiency. This issue indicates the relationship between vit A deficiency and decreased type 2 cytokine along with increased type 1 cytokine (24). It is presumed that the cause of non-significant increase of the mean of CD3+ in the vit A- receiving group in our study explains this inverse relationship.

In contrast to our results, in a study conducted by

Murphy et al. which performed on 89 women and 29 men over 65 years of age, it was showed that vit A supplementation of 800 μg/dl for 2 months could increase CD3+ T cell (25). The reasons for this difference might be the presence of immunologic factors in TB patients causing non significant alteration in blood CD3+ count or inadequate samples for detecting a significant difference in vit A- receiving group. Thus, it is recommended to use more samples.

Dawson et al. showed that the number of natural killer (NK) cells in mice with vit A deficiency were more than those with vit A supplementation (21). In a study conducted by Iwata et al. retinoic acid derivative was considered as Th2 system and plasma cell stimulator. This study was performed invitro on Th1/Th2 and showed that all-trans retinoic acid> 1nmol suppressed Th1 development while enhancing Th2 development.9-cis retinoic acid (9-cis RA) had also similar effect on all-trans form on development of the above mentioned systems (26).

As a conclusion, the immunologic response in TB patients is different comparing to non TB individuals. In some instances, our results are in contrary to other studies which may be due to a complex immunologic response, as the most important factor, to Mycobacterium tuberculosis itself, influencing expected results around vitamin A intensively.

Finally, regarding vit A influence on lymphocytic markers, further studies should be performed in order to use this vitamin for improving immune system.

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